Disulfiram revisited

Brian O'Shea

Disulfiram can be important in helping motivated alcoholics to remain abstinent. Prescribers should be aware of disulfiram's toxicity, and how to recognize and manage reactions. A number of other agents are available to help alcoholics remain sober, although these do not necessarily obviate use of disulfiram. Also, disulfiram may have a wider role in the management of the addictions, e.g. in cocaine use.

'In alcoholism, as in much of medicine, we dress the wound; we do not heal it' (Vaillant, 1999).

The size of the alcohol-related problem in society can be gauged from the fact that the Irish spent over IR£193million more in 1990 on alcohol than their government spent on the health services.

Alcohol (Al kihl, Arabic: essence) is broken down mainly via the alcohol dehydrogenase (ALDH; acetaldehyde-nicotinamide-adenine dinucleotide-oxidoreductase)/aldehyde dehydrogenase pathway. Deficiency of the active mitochondrial form of aldehyde dehydrogenase because of a base pair mutation in a single gene, found mainly but not exclusively in Orientals, predisposes to a 'flushing response' on ingesting alcohol and may protect against developing alcoholism (Harada et al, 1980; Marshall, 1990).

Disulfiram (Antabuse, Dumex, Barnstable), accidentally discovered by two medical doctors who were taking it while investigating its possible use as an antihelminthic, is a competitive, irreversible inhibitor of ALDH (which normally destroys alcohol-derived acetaldehyde), and its metabolite diethyldithiocarbamate (DEDC) inhibits dopamine-β-hydroxylase (which converts dopamine to noradrenaline).

'ANTABUSE' REACTIONS

The classic disulfiram–alcohol response leads to a hot, flushed face, injected sclerae, palpitations, dyspnoea, nausea, and headache lasting a few hours and tiring the patient. Acetaldehyde causes the release of histamine in the body. Anything containing alcohol can cause a reaction in the presence of disulfiram, e.g. lotions, medicinal syrups and alcohol-containing sweet drinks or 'alcopops' (McKeganey et al, 1996). Other causes of a disulfiram-like reaction include carbimide (Abstem, Temposil), chlorpropamine (Diabinese, a sulphonylurea), metronidazole (Flagyl), percutaneous absorption of the anti-scabetic monosulfiram (Tetmosol) (Staughton, 1996), cephamandole (a parenteral cephalosporin), and coprine (from the common ink cap mushroom *Coprinus atramentarius*). Flushing following alcohol of unknown mechanism has been reported with procarbazine, oral ketoconazole, and, in a single case, griseofulvin (Anonymous, 1996). Paraldehyde metabolism is blocked by disulfiram, with an accumulation of acetaldehyde.

A few other points should be noted in passing. Verapamil delays the elimination of alcohol, prolonging the effects of intoxication (which could be dangerous if driving), paracetamol hepatotoxicity is greater in chronic heavy drinkers because the breakdown of its metabolites is diminished, and binge-drinking while taking metformin increases the risk of lactic acidosis. The effects of combining sedative drugs with alcohol are well known.

EFFICACY

This has been hotly debated in the literature (Brewer, 1992; Hughes and Cook, 1997) with little in the way of consensus. A number of studies have failed to demonstrate differences between groups of patients taking disulfiram and those taking placebo (Fuller et al, 1986). Non-compliance has proved a major obstacle in providing support for disulfiram (Weinrieb and O'Brien, 1997). Compliance could be tested for by looking for diethylamine (urine) or carbon disulphide (breath) (Heather, 1989).

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Disulfiram implants failed to produce therapeutic levels (Johnsen et al, 1990).

TOXICITY

This may be difficult to distinguish from the toxic effects of chronic alcoholism (Webb, 1991). Toxicity is more likely in doses greater than 500 mg/day. A rare, dose-related, reversible mixed peripheral neuropathy may occur (Thrush, 1992), including optic neuritis (alcoholic neuropathy is mainly sensory). A psychosis may occur with clouded or clear consciousness; one possible mechanism is the inhibition of dopamine-β-hydroxylase by DEDC leading to increased dopamine concentration in the mesolimbic system (Ewing et al, 1977; Rossiter, 1992). In fact, an exacerbation of schizophrenia is potentially possible for the same reason.

Other problems include hepatotoxicity, tiredness, depression (possibly resulting from low noradrenaline levels), halitosis, a metallic or garlic-like taste, gastrointestinal upset, impotence, and the accumulation of nickel and lead. Disulfiram use during pregnancy has been associated with limb deformities in the fetus.

Contraindications include recent cardiac or marked liver disease, pregnancy, psychosis, coprescription of potent hypotensive drugs, or suicidal impulses.

OTHER APPROACHES

A number of approaches exist which may be used alone or in combination with disulfiram. Serotonin abnormalities have been implicated in many disorders, including alcoholism (Boyer and Feighner, 1992). Animal experiments and some clinical studies suggest that specific serotonin-reuptake inhibitors (SSRIs), e.g. fluoxetine, may reduce the craving for alcohol (Guimaraes, 1991). The 5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptor agonist and azapirone buspirone, marketed as an anxiolytic, may reduce the desire to drink in anxious alcoholic patients (Tollefson, 1991). Acamprosate (Campral, calcium bisacetyl homotaurinate, γ-aminobutyric acid (GABA) ergic and excitatory amino acid antagonist) reduces alcohol intake in both rats and humans (Paille et al, 1995; Sass et al, 1996; Whitworth et al, 1996; Pelc et al, 1997).

Naltrexone, an oral long-acting pure opiate antagonist (Brewer, 1986), may help some alcoholics to abstain, probably because of a role for opioid peptides in the motivation to drink (Scheepers, 1997). Citrated calcium carbimide, a reversible inhibitor of ALDH, was given as 50–100 mg/day. It is more rapidly metabolized that disulfiram and is less likely to produce adverse effects. It has no effect on dopamine-β-hydroxylase. Unfortunately, because of problems associated with the stability of the formulation leading to loss of potency over time, i.e. poor shelf-life, carbimide was removed from the Irish market in 1997.

DISULFIRAM IN PRACTICE

Disulfiram is prescribed most often by psychiatrists (generalist and specialist) and by general practitioners. It should never be given surreptitiously to a patient, although it can be supervised by a trusted other. It does not eliminate the urge to drink, except perhaps by psychological means. The former practice of deliberately inducing disulfiram–alcohol reactions to enlighten the patient is unsafe and probably unethical.

Disulfiram comes as 200 mg tablets. The anti-alcohol effect lasts at least 2 days after the last dose. The author feels that past criticisms that too low a dose was used and current recommendations for loading doses miss the crucial point: it is what the patient believes will happen if they drink that is important. The author prescribes disulfiram as 400 mg on Mondays, Wednesdays and Fridays. Only if liver function is greatly compromised is retesting advised some months hence before prescription should be considered. Most alcoholics will have mild/moderate liver function test (LFT) derangement that is not a contraindication to disulfiram treatment. A severe reaction can be terminated with ascorbic acid 1 g, given orally or intravenously, and an antihistamine (e.g. mepyramine maleate 25–50 mg) intravenously. LFTs should be monitored.

A few patients drink their way through a reaction and should have their prescription terminated. Some alcoholics take disulfiram to limit their alcohol intake, not to stop drinking completely, much as smokers use nicotine replacement formulations on long flights. The ethical problems for the prescriber are similar in both cases, although potentially more problematic in the former. Only very low doses should be prescribed for patients with schizophrenia or bipolar affective disorder, although some 'normal' people may be vulnerable to disulfiram-induced psychosis (Gerner, 1997).

Finally, there is some evidence that disulfiram may reduce cocaine use, probably by inhibition of dopamine-β-hydroxylase (Petrakis et al, 2000). HM

Conflict of interest: none.

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KEY POINTS

- Disulfiram is a competitive, irreversible enzyme inhibitor, leading to acetaldehyde accumulation. Acetaldehyde releases histamine.
- Disulfiram's metabolite causes an increase in dopamine availability.
- A classic disulfiram reaction consists of flushing, red eyes, palpitations, shortness of breath, nausea, and headache.
- Many other agents can cause a similar reaction, e.g. metronidazole.
- High doses may cause peripheral (including optic) neuropathy, psychosis, liver damage, fatigue, and depression; it is teratogenic.
- Specific serotonin release inhibitors (SSRIs), buspirone, and acamprosate are other strategies.
- For severe reactions give parenteral antihistamine and ascorbate.
- Cocaine use probably is reduced by disulfiram.